Remarks

Claims 30-35 remain pending in this application. Claims 30 and 32 were amended herein. The amendments were meant to more fully clarify the invention, and no new matter was added thereby. Applicants also respectfully assert that the amendments should be entered because the amendments do not raise issues that have not previously been considered by the Examiner. Favorable reconsideration is respectfully requested in light of the following comments.

35 U.S.C. § 102 Rejection

Claims 30, 32, 33, and 35 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Myers et al. (WO 95/15758) ("'758"). Applicants respectfully traverse this rejection.

The Examiner asserts that the phrase "UVB radiation-induced" could be viewed as a preamble and therefore does not limit the scope of the claim. Although Applicants do not concede the correctness of this position, claims 30 and 32 have been amended to more fully clarify that the inflammation is UVB radiation-induced. Applicants also respectfully submit that the treatment of autoimmune induced inflammation does not inherently disclose anything about the treatment of UVB radiation-induced inflammation. Applicants therefore respectfully assert that the '758 reference does not disclose all of the limitations of the currently pending claims, and therefore does not anticipate the claims. Applicants respectfully request the withdrawal of this rejection.

35 U.S.C. § 103 Rejection

Claims 30-35 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Myers et al. (WO 95/15758) ("'758"). Applicants respectfully traverse this rejection.

Applicants respectfully assert that one of skill in the art would not have been motivated to modify the teachings of '758 to obtain Applicants' invention because: 1) JAK-3 and CSF1-R function very differently and 2) autoimmune induced inflammation is a much different process than UVB radiation-induced inflammation.

Myers teaches the use of compounds of the genus for the inhibition of CSF-1R receptor tyrosine kinase. The Examiner states that it is "equally irrelevant whether the

compounds' modes of action are inhibition of JAK3 or CSF-1R." Applicants respectfully disagree. JAK3 and CSF-1R are significantly different, such that a teaching of autoimmune inflammation inhibition by targeting CSF-1R would not give one of skill in the art a reasonable expectation of success in treating UVB induced inflammation by targeting JAK3.

CSF-1R is a receptor tyrosine kinase expressed in low levels on cells of the neutrophilic lineage and in high levels on monocytes/macrophages (Kuby, 1994, *Immunology* 2d. Ed., at 50-52). CSF-1R has intrinsic ligand-inducible tyrosine kinase activity (Csar et al., 2001, *J. Bio. Chem.*, 276(28):26211). CSF-1R specifically interacts with CSF-1 and primarily plays a role in the activation of macrophages (Csar et al., *supra*).

In contrast, JAK-3 belongs to a small group of non-receptor tyrosine kinases (Yeh et al., 1999, *Cell. Mol. Life Sci.*, 55:1523). Its functions include transducing extra-cellular ligand-binding events for receptors with no intrinsic catalytic activity (Yeh et al., *supra*). Among their functions, JAKs function with receptors for both pro-inflammatory (e.g. IL-6) and con-inflammatory (e.g. IL-10) cytokines (Choy et al., 2001, *N. Engl. J. Med.*, 344(12):907; Hermanns et al., 2000, *J. Bio. Chem.*, 275(52):40742; Lalani et al., 1997, *Ann. Allergy Asthma. Immun.*, 79:469). In addition to playing a primary role in cytokine signaling, JAKs may also play accessory roles in other pathways (Yeh et al., *supra*). Rapid phosphorylation and activation of JAKs have been reported after stimulation with multiple growth factors whose receptors are known to possess intrinsic ligand-inducible tyrosine kinase activity (Yeh et al., *supra*).

In summary, the role of JAKs in the processes of inflammation is very complex such that one of skill in the art at the time of the invention would not have had any motivation to select the species of the claimed invention to treat UVB induced inflammation. Therefore, since JAK3 and CSF-1R are different and play different roles with respect to inflammation the disclosure of '758 related to treating autoimmune induced inflammation with a genus of compounds does not anticipate or make obvious the use of the particular species of the present invention for treatment of UVB radiation-induced inflammatory response. Applicants therefore respectfully request that the rejection be withdrawn.

The disclosure of '758 also does not render the present invention obvious because autoimmune induced inflammation is a much different process than is UVB radiation-induced inflammation. Therefore, compounds that might inhibit inflammation in the one may not inhibit inflammation in the other.

In UVB irradiated skin, upregulation of the expression by keratinocytes of IL-8 has been demonstrated (Boonstra, 1997, *European Cytokine Net.*, 8(2):117). The chemotactic properties of the enhanced expression of chemokines, such as IL-8, RANTES and IFN-gamma inducible protein 10, might contribute to the extensive infiltrates of macrophages and neutrophils that are observed in UVB irradiated skin (Boonstra, *supra*).

Conversely, autoimmune induced inflammation, such as in Hashimoto's Thyroiditis, is mediated by sensitized T_{DTH} cells which cause increased cytokine production that in turn leads to activation of macrophages (Kuby, *supra*, at 447). The DTH response is characterized by an intense infiltration of the affected tissue by lymphocytes, macrophages, and plasma cells, which form lymphocytic follicles and germinal centers (Kuby, *supra*, at 447).

Thus, because there are significant differences in the pathways leading to the two types of inflammation, one of skill in the art, without more, would not have a reasonable expectation that any particular species of the genus would have similar properties as anti-inflammatory agents for autoimmune induced and UVB radiation-induced inflammation. Therefore, the Myers reference does not anticipate or render obvious the species of the present invention and Applicants respectfully request that the rejection be withdrawn.

Conclusion

In view of the amendments and comments presented herein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested.

Respectfully submitted,
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Date: November 18, 2002

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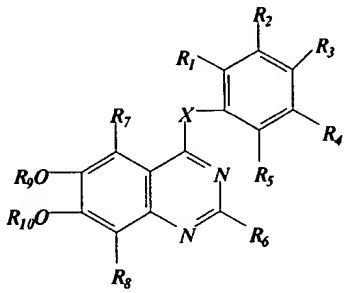
Version with Markings to Show Changes Made In the Claims

30. (Twice Amended) A method of treating [UVB radiation-induced] an inflammatory response in a mammal comprising administering to a mammal an effective amount of a compound of formula I:



wherein

X is selected from the group consisting of HN, $R_{11}N$, S, O, CH_2, and $R_{11}CH$;

R_{11} is $(C_1\text{-}C_4)$alkyl or $(C_1\text{-}C_4)$alkanoyl;

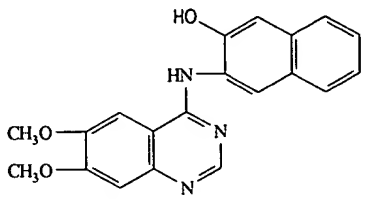
R_1 - R_5 are each independently selected from the group consisting of hydrogen, hydroxy and halo;

R_6, R_7, and R_8 are each independently selected from the group consisting of hydrogen, hydroxy, mercapto, amino, nitro, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_5)$alkylthio and halo; and

R_9 and R_{10} are each independently hydrogen, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo or (C1-C4)alkanoyl; or R_9 and R_{10} together are methylenedioxy; or a pharmaceutically acceptable salt thereof

wherein the inflammatory response to be treated is a UVB radiation-induced inflammatory response.

32. (Twice Amended) A method of treating [UVB radiation-induced] an inflammatory response in a mammal comprising administering to a mammal an effective amount of a compound having a structural formula:



wherein the inflammatory response to be treated is a UVB radiation-induced inflammatory response.